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Casimir Jones, S.C.
440 Science Drive
SUITE 203
Madison, WI 53711

EXAMINER	
THOMAS, DAVID C	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/728,486	ECKER ET AL.	
	Examiner	Art Unit	
	David C. Thomas	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-29,31-35,37,38,50-60,62-71,73-78 and 80-87* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-29,31-35,37,38,50-60,62-71,73-78 and 80-87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *14 May 2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 6, 2007 has been entered. Claims 27, 53, 69 and 75 (currently amended) and 28, 29, 31-35, 37, 38, 50-52, 54-60, 62-68, 70, 71, 73, 74, 76-78 and 80-87 (previously presented) will be examined on the merits. Claims 1-26, 30, 36, 39-49, 61, 72 and 79 were previously canceled.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 27, 28, 32-34, 36-38, 50, 69, 70, 73-76, 80, 81, 84 and 85 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hurst et al (Rapid Comm. Mass Spectrom. (1996) 10:377-382) in view of either Muddiman et al (Anal. Chem. (1997) 69:1543-1549) or Chen (U.S. Patent 6,613,509).

Hurst teaches a method of claims 27, 69 and 75 of identifying a pathogenic bioagent in sample (see page 377, column 1), comprising:

(a) contacting nucleic acid from said pathogen with a plurality of different primer pairs wherein at least one primer pair of said plurality of primer pairs hybridizes to flanking sequences of said nucleic acid, wherein said flanking sequences flank at least one variable nucleic acid sequence of said pathogen (see primers listed on page 378, table I, used for PCR performed using two sets of primer pairs, one directed to the 5S rRNA gene common to all species of the genus *Legionella* and one directed specifically to the *mip* gene fragment of *L. pneumophila,* page 378, column 1, lines 23-42);

(b) amplifying at least one of said variable nucleic acid sequences of said pathogen to produce at least one amplification product (PCR was performed for 30 cycles using two sets of primer pairs, one directed to the 5S rRNA gene and one directed to the *mip* gene fragment unique to *L. pneumophila* to produce 108- and 168-basepair products, respectively, see page 378, column 1, line 40 to column 2, line 13);

(c) *determining a base composition of said at least one amplification product wherein said base composition identifies said pathogen in said sample* (see page 379,

figure 1, where Hurst performs MALDI-TOF on both PCR products to determine base composition as the mass of the PCR product, and shows that this is a feasible method of detecting *Legionella*).

With regard to claims 28, 70, 81, Hurst teaches detection of a bacterial pathogen (see page 379, figure 1, where *Legionella* is detected).

With regard to claims 32-34, 76, Hurst teaches the use of specific primers that are genus and species specific (see page 378, table 1).

With regard to claim 36, Hurst teaches the base compositions of both the mip and 5S rRNA pcr products (see page 379, figure 1).

With regard to claims 37, 72, 73, 79, 80, Hurst teaches the use of MALDI-TOF (see abstract).

With regard to claims 38, 74, 84, Hurst teaches analysis of the 5S rRNA gene using primers directed to that gene (see page 378, table 1).

With regard to claims 50, 85, Hurst teaches analysis of the *mip* gene, which encodes a protein involved in virulence (see page 378, table 1).

Hurst does not determine the base composition by identifying the number of individual A, C, T, G and U residues, analogues thereof and mass tag residues thereof in the amplification product and does not compare said base composition to calculated or measured base compositions of analogous amplification products of one or more known pathogens present in a database comprising 5 or more base compositions.

Muddiman teaches analysis of base composition of PCR products of microorganisms wherein the base compositions identify the number of each individual A, C, T and G nucleotide present in the amplification products by mass spectrometry without sequencing the amplification products and wherein the base compositions identify the organism in the sample (see abstract, p. 1545, column 1, lines 30-40 and Figure 2). Muddiman exemplifies the base composition analysis in Table 1, showing the base compositions for a variety of PCR products, and the data is compared to expected composition, shown in Figure 3; the algorithm used is applicable to any mass-measured complementary DNA produced as PCR products using primer pairs flanking a targeted region of a bacterial geneome, and thus the sequence and base composition is known for unmutated strains, p. 1546, column 1, lines 3-9).

Chen also teaches analysis of base composition of PCR products of microorganisms wherein the base compositions identify the number of each individual nucleotide present in the amplification products without sequencing the amplification products and wherein the base compositions identify the organism in the sample (see claim 1, column 3, lines 6-21, and Table 3, wherein composition by numbers of A, T, C and G residues of PCR products are determined by mass spectrometry; composition determinations are compared to a reference standard, claim 1, column 3, lines 21-23 and Tables 2 and 3).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the Mass spectrometry base composition analysis

methods of Muddiman or Chen in the mass spectrometry analysis method of Hurst since Hurst expressly teaches mass spectrometric analysis of PCR products and since Muddiman expressly teaches "In this work, we have demonstrated that the complementary nature of DNA due to Watson-Crick base-pairing provides constraints that can be exploited in conjunction with the measured mass to allow determination of the number of base pairs and the base composition for relatively large DNA fragments. This approach uses accurate mass measurements and can be extended by the use of mass shifts induced by modified base PCR or postamplification modification, providing a rapid and accurate scheme by which to characterize PCR products of increasing size. This scheme should be particularly attractive for rapid confirmation of the base composition of PCR products (see page 1549, column 2)." An ordinary practitioner would have been motivated to improve the Hurst method by the use of the base composition analysis method of Muddiman in order to rapidly and accurately characterize the PCR products of Hurst down to the base composition level in order to confirm what sequence is present in the sample.

Further and distinct motivation to determine the base composition is provided by Chen, who notes "Using this technique, base compositions of DNA fragments have been determined with an accuracy of -/+0.03% with respect to their known sequences. The comparisons of base compositions among homologous sequences are useful in sequence validation, sequence comparison, and characterizations of sequence polymorphisms. In particular, the efficiency and accuracy of MALDI-TOF MS which provides analysis of molecular masses of short DNA molecules within seconds are

employed to obtain the base composition of a polymerase chain reaction (PCR) product solely from its molecular weight (see column 4, lines 45-56)." An ordinary practitioner would have been motivated to use the Chen method to determine the base composition in order to permit sequence comparisons in an efficient and accurate way using the mass spectrometric method of Hurst combined with the mass spectrometric and analysis methods of Chen.

Therefore, an ordinary practitioner, motivated to detect pathogens by Hurst, would have been motivated by both Muddiman and Chen to perform base-composition analysis in order to obtain the benefits of increased speed, accuracy without the requirement to use gel electrophoresis or other sequencing methods.

4. Claims 27-29, 31-35, 37, 38, 50-60, 62-71, 73-78 and 80-87 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoffman et al (Arch. Virol. (2001) 146:2275-2289) in view of Koster (WO 98/20166) and further in view of either Muddiman et al (Anal. Chem. (1997) 69:1543-1549) or Chen (U.S. Patent 6,613,509).

Hoffman teaches a method of claims 27, 53, 69 and 75 of identifying a pathogenic bioagent in sample (see page 2278, where influenza is the bioagent), comprising:

(a) contacting nucleic acid from said pathogen with a plurality of different primer pairs wherein at least one primer pair of said plurality of primer pairs hybridizes to flanking sequences of said nucleic acid, wherein said flanking sequences flank at least one variable nucleic acid sequence of said pathogen (see p. 2278, lines 1-32,

subheading "Design of oligonucleotides for RT-PCR", Table 1 and Figure 1, p. 2279, which detail a PCR reaction that was performed using eight sets of primer pairs binding to conserved regions each flanking the eight unique segments of the influenza virus);

(b) amplifying at least one of said variable nucleic acid sequences of said pathogen to produce at least one amplification product (two-step RT-PCR was performed using segment specific primers for the second step to amplify the reverse-transcribed products representing the eight segments of the influenza virus, p. 2278, lines 32-36 and Figure 2);

(c) determining a base composition of said at least one amplification product wherein said base composition identifies said pathogen in said sample (see page 2281, figure 3, where the base composition in terms of mass is determined by gel electrophoresis).

With regard to claims 28, 54, 70, 81, Hoffman teaches detection of a viral pathogen (see page 2281, figure 3, where Influenza virus is detected).

With regard to claims 29, 55, 71, 82, Hoffman teaches the use of tissue sample (see page 2277, where tissue from embryonated eggs is used and see page 2276, where virus isolation occurs from the throat of mammals).

With regard to claim 31, 56, 57, 83, Hoffman teaches that samples can be obtained from mammals and teaches the virus infects humans (see page 2276).

With regard to claims 32-34, 58-59, 76, Hoffman teaches the use of specific primers that are viral genus specific (see page 2278).

With regard to claim 35, 60, 77, 78, Hoffman teaches detection of viral subtypes using the primers (see figure 4, page 2282 and figure 5, page 2283 (and table 3) where primers specific for each subtype were used).

With regard to claims 38, 63, 74, 84, Hoffman teaches analysis of all of the genes of Influenza A, including any housekeeping genes (see page 2281, figure 2, where all of the eight segments of Influenza A are amplified).

With regard to claims 50, 51, 64, 65, 85, 86, Hoffman teaches analysis of all of the influenza A virus genes, including genes involved in virulence and the Influenza polymerase genes, PB1, PB2 and PA which form a heterotrimer (see page 2281, figure 2).

With regard to claim 66, 68, Hoffman teaches the use of eight primer pairs (see page 2281, figure 2).

With regard to claim 52, 67, 87, Hoffman teaches analysis "In pandemic situations where a new virus subtype emerges, we could either use the plasmid collection already available or quickly generate plasmids with the same or similar sequences, and use it to develop antiviral therapies (i.e., vaccines). Thus, a universal primer set is a powerful tool that can be used in classic and reverse genetics methods to prevent and contain future influenza A epidemics and pandemics (see page 2287)."

Hoffman teaches PCR to analyze and compare the viral subtypes but does not teach mass spectrometry or base composition signatures.

Koster teaches a method for detecting a single nucleotide polymorphism in an individual using molecular mass measurements such as MALDI TOF (page 14, for example), by determining the molecular mass of said amplification product using mass spectroscopy (page 13, line 1 and page 157, lines 10-29 and example 19) and comparing the molecular mass to the molecular mass of said region in an individual known to have said polymorphism, where if said molecular masses are the same then said individual has said polymorphism (page 13, lines 2-5 and page 158, lines 1-29, where Koster expressly compares patient 1 to a negative control and example 19).

With regard to claims 36, 37, 61, 62, 72, 73, 79 and 80, Koster expressly teaches comparison of base compositions with both modified and unmodified products wherein the base compositions identify the number of each individual nucleotide present in the amplification products without sequencing the amplification products and wherein the base compositions identify the organism in the sample (see page 66, for example, as well as page 105, table II and pages 69-70). At page 105, table II, Koster provides the base composition of three different PCR products determined by MALDI-TOF. Further, Koster specifically discusses using base composition to analyze mutations as discussed on page 70, where Koster notes "MS can also be used to determined full or partial sequences of larger DNAs; this can be used to detect, locate, and identify new mutations in a given gene region."

In particular, Koster expressly teaches the use of MALDI-TOF for diagnosis of bacterial or viral infections (see pages 73-79). Koster exemplifies this analysis in Example 5.

Muddiman teaches analysis of base composition of PCR products of microorganisms wherein the base compositions identify the number of each individual A, C, T and G nucleotide present in the amplification products by mass spectrometry without sequencing the amplification products and wherein the base compositions identify the organism in the sample (see abstract, p. 1545, column 1, lines 30-40 and Figure 2). Muddiman exemplifies the base composition analysis in Table 1, showing the base compositions for a variety of PCR products, and the data is compared to expected composition, shown in Figure 3; the algorithm used is applicable to any mass-measured complementary DNA produced as PCR products using primer pairs flanking a targeted region of a bacterial geneome, and thus the sequence and base composition is known for unmutated strains, p. 1546, column 1, lines 3-9).

Chen also teaches analysis of base composition of PCR products of microorganisms wherein the base compositions identify the number of each individual nucleotide present in the amplification products without sequencing the amplification products and wherein the base compositions identify the organism in the sample (see claim 1, column 3, lines 6-21, and Table 3, wherein composition by numbers of A, T, C and G residues of PCR products are determined by mass spectrometry; composition determinations are compared to a reference standard, claim 1, column 3, lines 21-23 and Tables 2 and 3).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the Mass spectrometry and base composition analysis method of Koster in the analytical method of Hoffman since Koster states "In another embodiment, an accurate sequence determination of a relatively large target nucleic acid, can be obtained by generating specifically terminated fragments from the target nucleic acid, determining the mass of each fragment by mass spectrometry and ordering the fragments to determine the sequence of the larger target nucleic acid (see page 75, line 26 to page 76, line 2)." So an ordinary practitioner would have been motivated to detect the PCR products of Muddiman with the base composition Mass spectrometric approach of Koster since Koster teaches that Mass Spectrometry is accurate and can improve the speed, mass accuracy and precision of the analysis (see Abstract, for example).

Further, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the Mass spectrometry base composition analysis methods of Muddiman or Chen in the mass spectrometry analysis method of Hoffman since Muddiman expressly teaches "In this work, we have demonstrated that the complementary nature of DNA due to Watson-Crick base-pairing provides constraints that can be exploited in conjunction with the measured mass to allow determination of the number of base pairs and the base composition for relatively large DNA fragments. This approach uses accurate mass measurements and can be extended by the use of mass shifts induced by modified base PCR or post-amplification modification, providing a rapid and accurate scheme by which to characterize PCR

products of increasing size. This scheme should be particularly attractive for rapid confirmation of the base composition of PCR products (see page 1549, column 2)." An ordinary practitioner would have been motivated to improve the Hoffman method by the use of the base composition analysis method of Muddiman in order to rapidly and accurately characterize the PCR products of Hoffman down to the base composition level in order to confirm what sequence is present in the sample.

Further and distinct motivation to determine the base composition is provided by Chen, who notes "Using this technique, base compositions of DNA fragments have been determined with an accuracy of -/+0.03% with respect to their known sequences. The comparisons of base compositions among homologous sequences are useful in sequence validation, sequence comparison, and characterizations of sequence polymorphisms. In particular, the efficiency and accuracy of MALDI-TOF MS which provides analysis of molecular masses of short DNA molecules within seconds are employed to obtain the base composition of a polymerase chain reaction (PCR) product solely from its molecular weight (see column 4, lines 45-56)." An ordinary practitioner would have been motivated to use the Chen method to determine the base composition in order to permit sequence comparisons in an efficient and accurate way using the PCR method of Hoffman combined with the mass spectrometric and analysis methods of Chen for analysis of PCR products.

Therefore, an ordinary practitioner, motivated to detect pathogens by Hoffman, would have been motivated by all of Koster, Muddiman and Chen to perform base

composition analysis in order to obtain the benefits of increased speed, accuracy without the requirement to use gel electrophoresis or other sequencing methods.

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 27-29, 31-35, 37, 38, 50-60, 62-71, 73-78 and 80-87 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-29 of U.S. Patent No. 7,108,974. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application claims represent a species of the current claims in which specific numbers of species are in the database and where specific mass is determined. Therefore, the

species of claims 1-29 of U.S. Patent No. 7,108,974 anticipates the current, more generic claims and renders them prima facie obvious.

7. Claims 27-29, 31-35, 37, 38, 50-60, 62-71, 73-78 and 80-87 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 7,226,739. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application claims represent a species of the current claims in which specific numbers of species are in the database and where specific mass is determined. Therefore, the species of claims 1-11 of U.S. Patent No. 7,226,739 anticipates the current, more generic claims and renders them prima facie obvious.

8. Claims 27-29, 31-35, 37, 38, 50-60, 62-71, 73-78 and 80-87 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-28 of U.S. Patent No. 7,255,992. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application claims represent a species of the current claims in which specific numbers of species are in the database and where specific mass is determined. Therefore, the species of claims 1-28 of U.S. Patent No. 7,255,992 anticipates the current, more generic claims and renders them prima facie obvious.

9. Claims 27-29, 31-35, 37, 38, 50-60, 62-71, 73-78 and 80-87 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 23-27, 30-34, 44-55 of copending Application No. 10/660,122. Although the conflicting claims are not identical, they are not patentably

distinct from each other because the copending application claims represent a species of the current claims in which specific numbers of species are in the database and where specific mass is determined. Therefore, the species of claims 23-27, 30-34, 44-55 of copending Application No. 10/660,122 anticipates the current, more generic claims and renders them prima facie obvious.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

10. Applicant's arguments filed August 6, 2007 have been fully considered but they are not persuasive.

Applicant then argues that the rejection of claims 27, 28, 32-34, 36-38, 50, 69, 70, 73-76, 80, 81, 84 and 85 under 35 U.S.C. § 103(a) as being obvious over Hurst in view of Muddiman or Chen and the rejection of claims 27-29, 31-35, 37, 38, 50-60, 62-71, 73-78 and 80-87 under 35 U.S.C. § 103(a) as being obvious over Hoffman in view of Koster and further in view of Muddiman or Chen should be withdrawn since there is no motivation to combine the cited references and there would be no expectation of success. Further, Applicant argues that the amended claims now contain elements of unexpected results beyond that of the cited prior art. Applicant also refers to a Declaration by Dr. Steven Buchsbaum that appears to be the same Declaration previously submitted in response to the Final Office Action of December 20, 2006, since no new Declaration appears in the record. A response to this Declaration was

presented in the previous Final Office Action of May 11, 2007 and will not be repeated here.

With regard to the amended claims, though additional elements relating to priming of a pathogen sequence by a plurality of primers and the comparison of base compositions to a database of compositions, the combination of the cited references teaches these limitations. For example, Hoffman teaches detection of eight different segments of a pathogen sequence wherein the mass of the PCR products are compared to standards. When combined with mass spectrometry measurements, the combined methods of Koster and Muddiman or Koster and Chen could be used to measure the unique sequence of each segment by determination of the base composition of each segment as compared to the known or expected mass.

With regard to Applicant's argument that there is no motivation to combine the cited references, Hurst provides motivation to design primers for detection of organisms other than *Legionella* using methods of mass spectrometry. Hurst concludes his article with "Mass spectrometry, especially MALDI-TOF MS, offers considerable, potential as a detection method for PCR-amplified bacterial DNA. Developments to extend the upper mass limit while decreasing the amount of material required are being pursued, along with improved rapid purification procedures." Hurst unambiguously motivates detection of bacterial DNA, not just *Legionella*. The absence of a specific teaching of other organisms does not detract from the motivation to detect and analyze other organisms. Muddiman and Chen teach base composition analysis that be used for detection of bacteria such as those taught by Hurst. In response to applicant's arguments against

the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

With regard to the 103 rejection over Hoffman in view of Koster, Muddiman and Chen, Koster provides motivation to use mass spectroscopy for measuring the PCR products taught by Hoffman by teaching that mass spectroscopy improves speed, accuracy and precision of the analysis. The Federal Circuit has recently provided a detail explanation of the subsidiary requirement for motivation to combine in Dystar v. Patrick Co., 80 USPQ 2d 1641, 1651(Fed. Cir. 2006) noting,

> "Indeed, we have repeatedly held that an implicit motivation to combine exists not only when a suggestion may be gleaned from the prior art as a whole, but when the "improvement" is technology-independent and the combination of references results in a product or process that is more desirable, for example because it is stronger, cheaper, cleaner, faster, lighter, smaller, more durable, or more efficient. Because the desire to enhance commercial opportunities by improving a product or process is universal-and even common-sensical-we have held that there exists in these situations a motivation to combine prior art references even absent any hint of suggestion in the references themselves. In such situations, the proper question is whether the ordinary artisan possesses knowledge and skills rendering him capable of combining the prior art references."

The Dystar court clarifies that motivation exists when the improvement results in a more desirable process and the issue then devolves to whether the ordinary artisan possesses the knowledge capable of combining the references. Here, where the ordinary practitioner is a Ph.D. with several years experience, there is no doubt that the ordinary artisan possesses the knowledge and motivation sufficient to use the

advantageous method of Koster with the method of Hoffman, Muddiman and Chen. Some of the listed motivations of Dystar, to result in a more efficient, faster and precise assay, are the precise sorts of motivation identified in Dystar.

With regard to expectation for success, the legal standard for "reasonable expectation of success" is provided by caselaw and is summarized in MPEP 2144.08, which notes "obviousness does not require absolute predictability, only a reasonable expectation of success; i.e., a reasonable expectation of obtaining similar properties. See , e.g. , In re O'Farrell , 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)." In this factual case, there is express teaching in the prior art of Hurst that PCR amplification and Mass spectrometric detection would function. There is further evidence as shown in Chen and Muddiman that one mode of Mass spectroscopic analysis is base composition analysis. These were not prophetic teachings by Hurst, Chen and Muddiman, but rather working examples on real world samples. This is sufficient for a reasonable expectation of success. The MPEP cites In re O'Farrell, which notes regarding "obvious to try" at page 1682, that,

> "In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. E.g ., In re Geiger , 815 F.2d at 688, 2 USPQ2d at 1278; Novo Industri A/S v. Travenol Laboratories, Inc ., 677 F.2d 1202, 1208, 215 USPQ 412, 417 (7th Cir. 1982); In re Yates , 663 F.2d 1054, 1057, 211 USPQ 1149, 1151 (CCPA 1981); In re Antonie , 559 F.2d at 621, 195 USPQ at 8-9. In others, what was "obvious to try" was to explore a new technology or general approach

> that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. In re Dow Chemical Co ., 837 F.2d, 469, 473, 5 USPQ2d 1529, 1532 (Fed. Cir. 1985); Hybritech, Inc. v. Monoclonal Antibodies, Inc ., 802 F.2d 1367, 1380, 231 USPQ 81, 90-91 (Fed. Cir. 1 986), cert. denied , 107 S.Ct. 1606 (1987); In re Tomlinson ; 363 F.2d 928, 931, 150 USPQ 623, 626 (CCPA 1966).

The court in O'Farrell then, affirming the rejection, notes " Neither of these situations applies here." For the instant case, it is clear that neither situations applies here either. This is not a situation where the prior art suggests varying a variety of parameters, since the prior art directly points to the use of base composition analysis in mass spectroscopy of PCR amplified DNA and teaches mass spectroscopic analysis of PCR amplicons derived from pathogenic bacteria. This is also not a situation where only general guidance was given. The prior art of Hurst, Chen and Muddiman provide specific guidance directing the use of mass spectroscopy for the analysis of PCR amplicons, including base composition analysis. For similar reasons, the prior art of Hoffman, Koster, Muddiman and Chen also provide a reasonable expectation of success. Therefore, for the reasons stated above, the 103 rejections are maintained.

Finally, with regard to double patenting, the rejections are revised to reflect recent issuances of U.S. Patent Nos. 7,108,974, 7,226,739 and 7,255,992.

Conclusion

11. Claims 27-29, 31-35, 37, 38, 50-60, 62-71, 73-78 and 80-87 are rejected. No claims are allowable.

Correspondence

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David C. Thomas whose telephone number is 571-272-3320 and whose fax number is 571-273-3320. The examiner can normally be reached on 5 days, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David C. Thomas 10/15/07
Patent Examiner
Art Unit 1637

/Young J. Kim/
Primary Examiner
Art Unit 1637
Technology Center 1600